Specification

Controlled-release oral preparation.

The Field of Technology

This invention relates to the following, namely, sustained release preparation for oral administration containing quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative.

Background Technique

In Japan patent bulletin 2647338, Kokai 6-293634, an uncoated tablet containing low melting lipid substance with improved abrasion resistance is disclosed. This uncoated tablet has the excellent property that the said abrasion resistance was improved, but the properties of disintegration and elution are both high. However, when uncoated tablet containing drug was administered orally, there are cases in which high blood concentration of drug is exhibited due to the release of the contained drug is released in gastrointestinal tract all at once.

Drugs, such as arthritis therapeutic agent such as anti inflammatory, antirheumatic drug, osteogenesis accelerating agent and prevention / therapeutic agent or the like of disease thought to be related to immunity, are being sought which can be used over the long term. By making release from preparation continuous, to make the blood concentration after oral administration smooth, it should be possible to reduce side effects and exhibit sufficient action effect.

Disclosure of the Invention

These inventors carried out assiduous investigations in order to achieve continued release from preparation, and smoothed blood concentration after oral administration. As a result, they discovered that as a result of including a gel-forming substance, and in addition, if required, a disintegration agent, especially a saccharide, in a quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative, the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative have satisfactory sustained-release. This invention was completed based on this finding, and the results of further study.

This invention relates to the following, namely:

(1) sustained-release oral preparation containing (i) quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives and (ii) a gel forming substance.

(2) preparation in accordance with aforesaid (1), wherein the quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives have antiinflammatory action or antirheumatic action.

(3) preparation in accordance with aforesaid (1), wherein a disintegration aid is further contained.

(4) preparation in accordance with aforesaid (1), wherein the gel forming substance is a water-soluble polymer compound.

(5) preparation in accordance with aforesaid (4), wherein the water-soluble polymer compound is a cellulose derivative, polyvinyl-series polymer compound or polyhydric alcohol.

(6) preparation in accordance with aforesaid (4), wherein the water-soluble polymer compound is hydroxypropylmethylcellulose.

(7) preparation in accordance with aforesaid (3), wherein the disintegration aid is a saccharide.

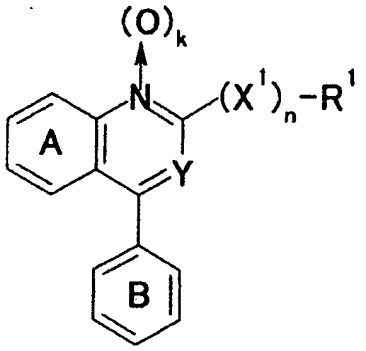
(8) preparation in accordance with aforesaid (7), wherein the saccharide is a sugar alcohol.

(9) preparation in accordance with aforesaid (1), wherein the weight ration of (i) quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives : (ii) gel forming substance is about 1 : about 0.1-100.

(10) preparation in accordance with aforesaid (3), wherein weight ratio of (i) quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives : (ii) gel forming substance : (iii) disintegration aid is about 1 : about 0.1-50 : about 0.01-50.

(11) preparation in accordance with the aforesaid (1), wherein the gel forming substance is formulated by about 10 wt.% or more with respect the whole preparation.

(12) preparation in accordance with the aforesaid (1), wherein the quinoline or quinazoline derivative is a compound represented by formula



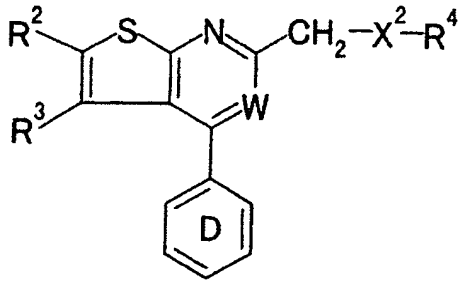
[I]

[in the formula, Y denotes a nitrogen atom or C-G (G denotes a carboxyl group which may be esterified or amidated, optionally substituted acyl group, optionally protected hydroxyalkyl group or halogen atom), R1 denotes an optionally substituted hydrocarbon group or optionally substituted heterocyclic group, X1 denotes an oxygen atom or optionally oxidised sulphur atom, n denotes 0 or 1, and k denotes 0 or 1. G and R1 may be linked to each other to form a ring. Ring A and Ring B may each have substitute group] or a salt thereof.

(13) preparation in accordance with the aforesaid (12), wherein Y is C-G'' (G'' denotes a carboxyl group which may be esterified), R1 denotes a C1-4 alkyl group substituted by an optionally substituted nitrogen-containing unsaturated heterocyclic group (wherein, the nitrogen-containing unsaturated heterocyclic group is bonded to said C1-4 alkyl group at its constituent nitrogen atom), n is 0.

(14) preparation in accordance with the aforesaid (13), wherein the quinoline or quinazoline derivative is ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl) quinoline-3-carboxylate.

(15) preparation in accordance with the aforesaid (1), wherein the thienopyridine or thienopyrimidine derivative is a compound represented by formula



[II]

[in the formula, R2 and R3 may be the same or different and denote a hydrogen atom, halogen atom or optionally substituted alkyl group, and R2 and R3 may be linked to form an optionally substituted

5- to 7-membered ring. W denotes a nitrogen atom or a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified, or a halogen atom), X2 denotes an oxygen atom, optionally oxidised sulphur atom or a group represented by formula -(CH2)q- (wherein, q is an integer of 0-5), R4 denotes an optionally substituted heterocyclic group or optionally substituted amino group. The D ring may be substituted], or a salt thereof.

(16) preparation in accordance with the aforesaid (15), wherein in the thienopyridine or thienopyrimidine derivative, R2 and R3 are linked to form an optionally substituted 5- to 7-membered ring, W is a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified or a halogen atom), R4 is an optionally substituted heterocyclic ring.

(17) A method to control the release of quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives by formulation of a gel forming substance in an oral preparation containing quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives.

(18) use of a gel forming substance for the production of a sustained release preparation containing quinoline or quinazoline derivatives or thienopyridine or thienopyrimidine derivatives,

(19) process in accordance with the aforesaid (17) wherein the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative is the compound that has antiinflammatory action or antirheumatic action,

(20) process for controlling the release of quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative in oral preparation containing quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative comprising formulating a gel-forming substance and disintegration aid ,

(21) process in accordance with the aforesaid (17) wherein gel-forming substance is water-soluble polymer compound,

(22) process in accordance with the aforesaid (21) wherein the water-soluble polymer compound is cellulose derivative, polyvinyl system polymer or polyvalent alcohol,

(23) process in accordance with the aforesaid (21) wherein the water-soluble polymer compound is hydroxypropyl methyl cellulose,

(24) process in accordance with the aforesaid (20) wherein the disintegration aid is saccharide.

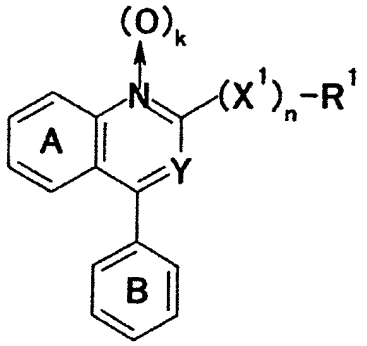
(25) process in accordance with the aforesaid (24) wherein the saccharide is sugar alcohol.

(26) process in accordance with the aforesaid (17) wherein the weight ratio of (i) quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative : (ii) gel-forming substance is about 1 : about 0.1-100,

(27) process in accordance with the aforesaid (20) wherein the weight ratio of (i) quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative: (ii) gel-forming substance : (iii) disintegration aid is about 1: about 0.1-50 : about 0.01-50,

(28) process in accordance with the aforesaid (17) wherein gel-forming substance is formulated at about 10 wt.% or more with respect to the whole preparation,

(29) process in accordance with the aforesaid (17) wherein quinoline or quinazoline derivative is a compound represented by formula



[I]

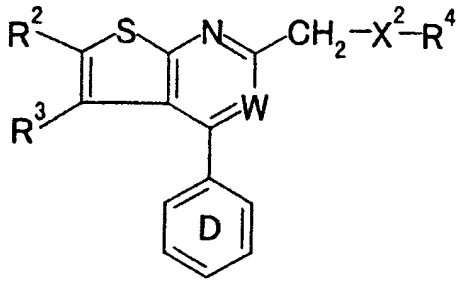
[in the formula, Y denotes a nitrogen atom or C-G (G denotes a carboxyl group which may be esterified or amidated, optionally substituted acyl group, optionally protected hydroxyalkyl group or halogen atom), R1 denotes an optionally substituted hydrocarbon group or optionally substituted heterocyclic group, X1 denotes an oxygen atom or optionally oxidised sulphur atom, n denotes 0 or 1, and k denotes 0 or 1. G and R1 may be linked to each other to form a ring. Ring A and Ring B may each have substitute group] or a salt thereof,

(30) process in accordance with (29), wherein Y is C-G'' (G'' denotes a carboxyl group which may be esterified), R1 denotes a C1-4 alkyl group substituted by an optionally substituted nitrogen-containing

unsaturated heterocyclic group (wherein, the nitrogen-containing unsaturated heterocyclic group is bonded to said C1-4 alkyl group at its constituent nitrogen atom), n is 0,

(31) process in accordance with the aforesaid (30) wherein the quinoline derivative or quinazolines is ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl) quinoline-3-carboxylate.

(32) process in accordance with the aforesaid (17), wherein the thienopyridine or thienopyrimidine derivative is a compound represented by formula



[II]

[in the formula, R2 and R3 may be the same or different and denote a hydrogen atom, halogen atom or optionally substituted alkyl group, and R2 and R3 may be linked to form an optionally substituted 5- to 7-membered ring. W denotes a nitrogen atom or a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified, or a halogen atom), X2 denotes an oxygen atom, optionally oxidised sulphur atom or a group represented by formula -(CH2)q- (wherein, q is an integer of 0-5), R4 denotes an optionally substituted heterocyclic group or optionally substituted amino group. The D ring may be substituted], or a salt thereof,

(33) process in accordance with the aforesaid (32), wherein, in the thienopyridine or thienopyrimidine derivative, R2 and R3 are linked to form an optionally substituted 5- to 7-membered ring, W is a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified or a halogen atom), R4 is an optionally substituted heterocyclic ring,

(34) use in accordance with the aforesaid (18) wherein the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative is a compound that has antiinflammatory action or antirheumatic action,

(35) use of a gel-forming substance and disintegration aid to produce sustained release preparation containing quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative.

(36) use in accordance with the aforesaid (18) wherein the gel-forming substance is water-soluble polymer compound,

(37) use in accordance with the aforesaid (36) wherein the water-soluble polymer compound is cellulose derivative, polyvinyl system polymer or polyvalent alcohol,

(38) use in accordance with the aforesaid (36) wherein the water-soluble polymer compound is hydroxypropyl methyl cellulose,

(39) use in accordance with the aforesaid (35) wherein the disintegration aid is saccharide,

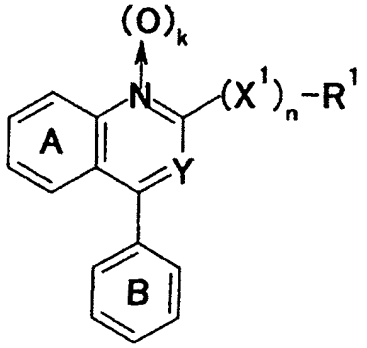
(40) use in accordance with the aforesaid (39) wherein the saccharide is a sugar alcohol,

(41) use in accordance with the aforesaid (18) wherein the weight ration of (i) quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative : (ii) gel-forming substance is about 1 : about 0.1-100,

(42) use in accordance with the aforesaid (18) wherein the weight ratio of (i) quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative : (ii) gel-forming substance : (iii) disintegration aid is about 1 : about 0.1-50 : about 0.01-50,

(43) use in accordance with the aforesaid (18) wherein the gel-forming substance is about 10 wt.% or more with respect to the whole preparation,

(44) use in accordance with the aforesaid (18) wherein quinoline or quinazoline derivative is a compound represented by formula



[I]

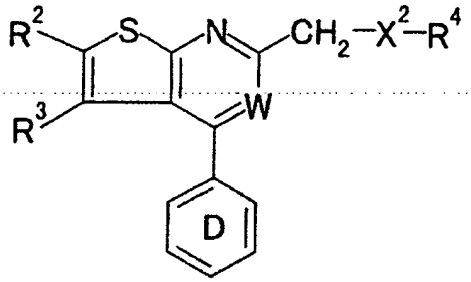
[in the formula, Y denotes a nitrogen atom or C-G (G denotes a carboxyl group which may be esterified or amidated, optionally substituted acyl group, optionally protected hydroxyalkyl group or

halogen atom), R1 denotes an optionally substituted hydrocarbon group or optionally substituted heterocyclic group, X1 denotes an oxygen atom or optionally oxidised sulphur atom, n denotes 0 or 1, and k denotes 0 or 1. G and R1 may be linked to each other to form a ring. Ring A and Ring B may each have substitute group] or a salt thereof,

(45) use in accordance with aforesaid (14), wherein Y is C-G'' (G'' denotes a carboxyl group which may be esterified), R1 denotes a C1-4 alkyl group substituted by an optionally substituted nitrogen-containing unsaturated heterocyclic group (wherein, the nitrogen-containing unsaturated heterocyclic group is bonded to said C1-4 alkyl group at its constituent nitrogen atom), n is 0,

(46) use in accordance with the aforesaid (45) wherein the quinoline derivative or quinazolines is ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl) quinoline-3-carboxylate,

(47) use in accordance with the aforesaid (18), wherein the thienopyridine or thienopyrimidine derivative is a compound represented by formula



[II]

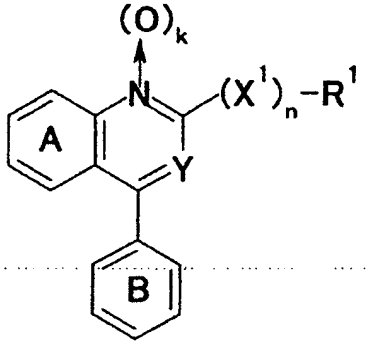
[in the formula, R2 and R3 may be the same or different and denote a hydrogen atom, halogen atom or optionally substituted alkyl group, and R2 and R3 may be linked to form an optionally substituted 5- to 7-membered ring. W denotes a nitrogen atom or a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified, or a halogen atom), X2 denotes an oxygen atom, optionally oxidised sulphur atom or a group represented by formula -(CH2)q- (wherein, q is an integer of 0-5), R4 denotes an optionally substituted heterocyclic group or optionally substituted amino group. The D ring may be substituted], or a salt thereof, and

(48) Use in accordance with the aforesaid (18), wherein, in the thienopyridine or thienopyrimidine derivative, R2 and R3 are linked to form an optionally substituted 5- to 7-membered ring, W is a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified or a halogen atom), R4 is an optionally substituted heterocyclic ring.

Ideal form for Carrying Out the Invention

The quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative contained in sustained-release oral preparation of this invention may be any which can be used as drug. As these derivatives, the compound having antiinflammatory action (more particularly anti arthritis action), antirheumatic action, bone resorption inhibitory action, immunomodulation action, and/or immunologic cytokine (for example interleukin-2 (IL-2), interferon-γ (IFN-γ)) production inhibitory action is preferred.

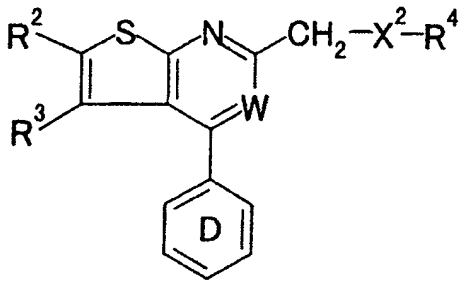
As embodiment of quinoline or quinazoline derivative contained in sustained-release oral preparation of this invention, for example compound represented by formula (I)



[I]

[in the formula each group has the same aforesaid meaning] or salts thereof may be proposed.

As embodiment of thienopyridine or thieno pyrimidine derivative contained in sustained-release oral preparation of this invention, for example compound represented by formula (II)



[II]

[in the formula each group has the same aforesaid meaning] or salts thereof may be proposed.

In the aforesaid formula (I), aliphatic hydrocarbon residue, alicyclic hydrocarbon residue, alicyclic - aliphatic hydrocarbon residue, aromatic carbocyclic-aliphatic hydrocarbon residue, aromatic

hydrocarbon residue and the like may be proposed as the hydrocarbon residue and in optionally substituted hydrocarbon residue represented by R1.

As said aliphatic hydrocarbon residue, saturated aliphatic hydrocarbon residue of carbon number 1-10 (for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl or the like), unsaturated aliphatic hydrocarbon residue of 2-10 C (for example 2-10C-alkenyl group, 2-10C alkynyl group are proposed. For example as embodiment thereof, vinyl (ethenyl), allyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethinyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl, 1-octynyl or the like) are proposed.

As said alicyclic hydrocarbon residue, saturated alicyclic hydrocarbon residue of carbon number 3-8 (for example, 3-8C cycloalkyl group is proposed, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or the like) is proposed as embodiment thereof, further more, C7-10 bicycloalkyl group (for example, bicyclo[2,2,1]heptyl, bicyclo[2,2,2] octyl, bicyclo[3,2,1] octyl, bicyclo [3,2,2] nonyl, bicyclo[3,3,1] nonyl, bicyclo[4,2,1] nonyl, bicyclo[4,3,1] decyl and the like) are proposed, and unsaturated alicyclic hydrocarbon residue of 5-8 C (for example, 5-8C cycloalkenyl group, 5-8C cycloalkadienyl group are proposed, as embodiments for example 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2,4-cyclopentadienyl, 2,4-cyclohexadienyl, 2,5-cyclohexadienyl, 2,4-cycloheptadienyl or the like) are proposed.

As said alicyclic-aliphatic hydrocarbon residue, the ones of carbon number 4-9 among the ones wherein the aforesaid alicyclic hydrocarbon residue was combined with the aforesaid aliphatic hydrocarbon residue (for example cyclopropylmethyl, cyclopropylethyl, cyclobutyl methyl, cyclopentylmethyl, 2-cyclopentenyl methyl, 3-cyclopentenyl methyl, cyclohexylmethyl, 2-cyclohexenyl methyl, 3-cyclohexenyl methyl, cyclohexyl ethyl, cyclohexyl propyl, cycloheptyl methyl, cycloheptyl ethyl or the like).

As said aromatic carbocyclic-aliphatic hydrocarbon residue, 7-9C phenylalkyl (for example benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, 1-phenylpropyl or the like), naphthylalkyl of 11-13C (for example α-naphthylmethyl, α-naphthyl ethyl, β-naphthylmethyl, β-naphthyl ethyl or the like) may be proposed.

As said aromatic hydrocarbon residue, 6-14C aryl such as phenyl, naphthyl (for example, α-naphthyl, β-naphthyl), anthryl, phenanthryl, acenaphthylenyl or the like may be proposed.

In the aforesaid formula (I), as optionally substituted heterocyclic group represented by R1, for example (i) 5-7 membered heterocyclic group including one sulfur, nitrogen or oxygen atom, (ii) 5-6 membered heterocyclic group including 2-4 nitrogen atoms, (iii) 5-6 membered heterocyclic group including 1-2 nitrogen atoms and one oxygen or sulfur atom may be proposed and (iv) these heterocyclic groups may be condensed with 6-membered ring containing 2 or less nitrogen atoms, benzene ring, or 5-membered ring containing one sulfur atom. Moreover, it may be non-aromatic aliphatic heterocyclic group.

As embodiment of said heterocyclic group, for example (1) 5 membered heterocyclic group which includes 1-4 heteroatoms selected from the oxygen atom, sulfur atom, nitrogen atom in addition to carbon atom, for example, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl and the like,
(2) 6 membered heterocyclic group which includes 1-4 heteroatoms that were selected from the oxygen atom, sulfur atom, nitrogen atom in addition to carbon atoms, for example pyridyl, pyrimidinyl, thiomorpholinyl, morpholinyl, oxoimidazinyl (sic), triazinyl, pyrrolidinyl, piperidinyl, pyranyl,-thio pyranyl, 1,4-oxazinyl, 1,4, thiazinyl, 1,3-thiazinyl, piperazinyl, triazinyl, oxo triazinyl, 3- or 4-pyridazinyl, pyrazinyl, 3- or 4-pyridazinyl and the like.

(3) bicyclic or tricyclic fused heterocycle group including 1-4 heteroatoms selected from oxygen atom, sulfur atom, nitrogen atom in addition to carbon atom, for example benzofuranyl, isobenzofuranyl, benzo (b) thienyl, benzothiazolyl, benzo isothiazolyl, benzoxazolyl, benzo isoxazolyl, benzotriazolyl, tetrazolo [1,5-b] pyridazinyl, triazolo [4,5-b] pyridazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolyl, isoindolyl, indolizinyl, quinolidinyl, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, α-, β- or γ-carbolinyl, acridinyl, phenanthridinyl, chromanyl, benzo oxazinyl, phenazinyl, phenoxazinyl, phenothiazinyl, phenoxathienyl, thianthrenyl, phenathridinyl (sic), phenathrolinyl (sic), 1H-indazol-3-yl, 1H-indazol-1-yl, 1H-pyrrolo (2,3-b) pyrazine-2-yl, 1H-pyrrolo (2,3-b) pyridine-6-yl, pyrrolo (1,2-b) pyridazinyl, pyrazolo [1,5-a] pyridyl, 1H-imidazo (4,5-b) pyridine-2-yl, 1H-imidazo (4,5-c) pyridine-2-yl, imidazo (1,2-a) pyridyl, imidazo (1,5-a) pyridyl, imidazo (1,2-b) pyridazinyl, imidazo (1,2-a) pyrimidinyl. 1H-imidazo (4,5-b) pyrazine-2-yl, 1H-pyrrolo (1,2-a) imidazol-1-yl,

1H-pyrrolo (1,2-b) (1,2,4) triazol-1-yl, 1,8a-dihydroimidazo (1,2-a) pyridin-1-yl, 7-purinyl, 3,3a-dihydro (1,2,4) triazolo (1,5-a) pyrimidine-3-yl, 1H-pyrazolo (4,3-d) oxazol-1-yl, 4H-imidazo (4,5-d) thiazol-4-yl, 1,2,4-triazolo (4,3-a) pyridyl, 1,2,4-triazolo (4,3-b) pyridazinyl, 1,8a-dihydro (1,2,4) triazolo (1,5-a) pyridin-1-yl, 3,3a-dihydro (1,2,4) triazolo (1,5-a) pyrimidine-3-yl, 1,8a-dihydroimidazo (1,2-a) pyrimidine-1-yl, 1H-pyrazolo (4,3-d) oxazol-1-yl, 4H-imidazo (4,5-d) thiazol-4-yl, and the like may be proposed.

As ideal example of said non-aromatic aliphatic heterocyclic group, 3-7 membered heterocyclic group including 1-4 sulfur, nitrogen or oxygen atoms is proposed. Oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like may be proposed.

Hydrocarbon residue or heterocyclic group represented by R1 in the aforesaid formula (I) may have 1-3 substituents at arbitrary substitutable positions in chain or ring thereof. As such substituent, for example aliphatic chain hydrocarbon group, alicyclic hydrocarbon group, aryl group, aromatic heterocyclic ring group, non-aromatic aliphatic heterocyclic group, halogen atom, nitro group, optionally substituted amino group, optionally substituted acyl group, optionally substituted hydroxy group, optionally substituted thiol group, optionally esterified carboxyl group, amidino group, carbamoyl group, sulphamoyl group, sulfo group, cyano group, azido group, nitroso group, oxo group and the like may be proposed.

As aliphatic chain hydrocarbon group as said substituent, aliphatic hydrocarbon group of branched chain or straight chain, for example alkyl group (preferably 1-10C alkyl group), alkenyl group (preferably 2-10C alkenyl group), alkynyl group (preferably 2-10C alkynyl group) may be proposed.

As ideal example of said alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert pentyl, 1-ethyl propyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,-3-dimethylbutyl, 2-ethyl butyl, hexyl, pentyl, octyl, nonyl, decyl and the like may be proposed.

As ideal example of said alkenyl group, for example, vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl and the like may be proposed.

As ideal example of said alkynyl group, for example, ethinyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like may be proposed.

As alicyclic hydrocarbon group as said substituent, saturated or unsaturated 3-10C alicyclic hydrocarbon group (for example 3-10C cycloalkyl group, 3-8C cycloalkenyl group, 4-8C cycloalkadienyl group or the like) may be proposed.

As ideal example of said 3-10C cycloalkyl group, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo (2.2.1) heptyl, bicyclo (2.2.2) octyl, bicyclo (3.2.1) octyl, bicyclo (3.2.2) nonyl, bicyclo (3.3.1) nonyl, bicyclo (4.2.1) nonyl, bicyclo (4.3.1) decyl and the like may be proposed.

As ideal example of said 3-8C cycloalkenyl group, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl or the like are proposed. Among these 5-7 C cycloalkenyl group is preferred.

As ideal example of said 4-8C cycloalkadienyl group, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl, 2,5-cyclohexadien-1-yl or the like are proposed. Among these 5-7C cycloalkadienyl group is preferred.

As aryl group as said substituent, a monocyclic or condensed polycyclic aromatic hydrocarbon group of 6-14 C is preferred, and for example phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl or the like is proposed as ideal example. Among these phenyl, 1-naphthyl, 2-naphthyl or the like are preferred.

As ideal example of aromatic heterocyclic ring group as said substituent, (i) 5-7 membered heterocyclic group including one sulfur, nitrogen or oxygen atom, (ii) 5-6 membered heterocyclic group including 2-4 nitrogen atoms, (iii) 5-6 membered heterocyclic group including 1-2 nitrogen atoms and one oxygen or sulfur atom may be proposed, and as aromatic monocyclic heterocyclic group, for example, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl or the like are proposed.

(iv) as the aromatic condensed heterocyclic group wherein a 6-membered ring containing 2 or less nitrogen atoms, benzene ring, or 5-membered ring containing one sulfur atom is condensed, for example, benzofuranyl, isobenzofuranyl, benzo (b) thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzo isoxazolyl, benzothiazolyl, 1,2-benzo isothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathienyl, thianthrenyl, phenathridinyl (sic), phenathrolinyl (sic), indolizinyl, pyrrolo (1,2-b) pyridazinyl, pyrazolo (1,5-a) pyridyl, imidazo (1,2-a) pyridyl, imidazo (1,5-a) pyridyl, imidazo (1,2-b) pyridazinyl, imidazo (1,2-a)-pyrimidinyl, 1,2,4-triazolo (4,3-a) pyridyl, 1,2,4-triazolo (4,3-b) pyridazinyl and the like may be proposed.

As ideal example of non-aromatic aliphatic heterocyclic group as said substituent, 3-7 membered heterocyclic group including 1-4 sulfur, oxygen or nitrogen atom is proposed, and oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl and the like may be proposed.

As example of halogen as said substituent, fluorine, chlorine, bromine and iodine are proposed. More particularly fluorine and chlorine are preferred.

As optionally substituted amino group, (i) amino groups, and (ii) substituted amino group [amino group substituted by 1 or 2 susbtituents of 1-10C alkyl, 2-10 C alkenyl, 2-10 C alkynyl, 1-10 C acyl group, 6-12 C aromatic group, heterocyclic group may be proposed (for example methylamino, dimethylamino, ethylamino, diethylamino, dibutyl amino, diallyl amino, cyclohexyl amino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionyl amino, benzoylamino, nicotinoyl amino and the like] may be proposed.

As the optionally substituted acyl group as said substituent, (i) formyl and (ii) the one wherein carbonyl is bonded to 1-10C alkyl, 2-10 C alkenyl or aromatic group (for example acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutane carbonyl, cyclopentane carbonyl, cyclohexane carbonyl, cycloheptane carbonyl, crotonyl, 2-cyclohexene carbonyl, benzoyl, nicotinoyl and the like) may be proposed.

As the optionally substituted hydroxy group as said substituent, (i) hydroxy group and (ii) hydroxy group having suitable substituent, particularly one used as a protecting group of hydroxy group (for example alkoxy, alkenyloxy, alkynyl oxy, aralkyloxy, acyloxy, aryloxy or the like) may be proposed.

As said alkoxy, 1-10C alkoxy (for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso butoxy, sec-butoxy, tert butoxy, pentyloxy, isopentyloxy, neopentyl oxy, hexyloxy, heptyl oxy, nonyl oxy, cyclobutyl oxy, cyclopentyl oxy, cyclohexyl oxy and the like) is preferred.

As said alkenyloxy, 2-10C alkenyloxy (for example allyloxy, crotyl oxy, 2-pentenyl oxy, 3-hexenyl oxy, 2-cyclopentenyl methoxy, 2-cyclohexenyl methoxy and the like) is preferred.

As said alkynyl oxy, 2-10C alkynyl oxy (for example ethinyl oxy, 2-propynyl oxy and the like) is preferred.

As said aralkyloxy, for example phenyl-C1-4 alkyloxy (for example, benzyloxy, phenethyl oxy or the like) may be proposed.

As said acyl oxy, 2-4C alkanoyloxy (for example, acetyl oxy, propionyloxy, butyryl oxy, isobutyryl oxy and the like) are preferred.

As said aryloxy, phenoxy, 4-chlorophenoxy and the like may be proposed.

As the optionally substituted thiol group as said substituent, the thiol group and the thiol group having suitable substituent, particularly protecting group of thiol group, (for example alkylthio, alkenyl thio, alkynyl thio, aralkyl thio, acylthio, arylthio or the like) may be proposed.

As said alkylthio, 1-10C alkylthio (for example methylthio, ethylthio, propylthio, isopropylthio, butyl thio, isobutyl thio, sec-butylthio, tert-butylthio, pentyl thio, isopentyl thio, neopentyl thio, hexyl thio, heptyl thio, nonyl thio, cyclobutyl thio, cyclopentyl thio, cyclohexyl thio and the like) is preferred.

As said alkenyl thio, 2-10C alkenyl thio (for example allyl thio, crotyl thio, 2-pentenyl thio, 3-hexenyl thio, 2-cyclopentenyl methylthio, 2-cyclohexenyl methylthio and the like) is preferred.

As said alkynyl thio, 2-10C alkynyl thio (for example ethinyl thio, 2-propynyl thio and the like) is preferred.

As said aralkyl thio, for example phenyl-C1-4 alkylthio (for example, benzylthio, phenethyl thio and the like) may be proposed.

As said acylthio, 2-4C alkanoyl thio (for example, acetylthio, propionyl thio, butyryl thio, isobutyryl thio and the like) are preferred.

As said arylthio, phenylthio, 4-chlorophenylthio and the like may be proposed.

As the carboxyl group which may be esterified which was shown as said substituent (i) carboxyl group, or (ii) one wherein 1-6C alkyl group is bonded to carboxyl group (namely, alkoxycarbonyl, for example methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxycarbonyl, isobutoxy carbonyl, sec butoxycarbonyl, tert butoxycarbonyl, pentyl oxycarbonyl, hexyl oxycarbonyl and the like), (iii) one wherein 3-6C alkenyl group is bonded to carboxyl group (namely, alkenyl oxycarbonyl, for example allyl oxycarbonyl, crotyl oxycarbonyl, 2-pentenyl oxycarbonyl, 3-hexenyl oxycarbonyl and the like) and (iv) one wherein aralkyl group is bonded to carbonyl group (namely, aralkyl oxycarbonyl, for example benzyl oxycarbonyl, phenethyl oxycarbonyl and the like) may be proposed.

In the aforesaid formula (I), the substituent in the hydrocarbon residue or heterocyclic group represented by R1, may furthermore have 1 or more, preferably 1-3, suitable substituents in respectively arbitrary substitutable positions. As such substituent, for example 1-10C alkyl group, 2-10C alkenyl group, 2-10C alkynyl group, 3-8C cycloalkyl group, 3-8C cycloalkenyl group, 4-8C cycloalkadienyl group, aryl group, aromatic heterocyclic ring group, non-aromatic aliphatic heterocyclic group, aralkyl group (for example aryl 1-6C alkyl group and the like), amino group, N-mono substituted amino group, N,N-disubstituted amino group, amidino group, acyl group, carbamoyl group, N-mono substituted carbamoyl group (for example, methylcarbamoyl, ethyl carbamoyl, phenylcarbamoyl and the like), N,N-disubstituted carbamoyl group (N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, piperidino carbamoyl, morpholino carbamoyl and the like), sulphamoyl group, N-mono substituted sulphamoyl group (for example methyl sulphamoyl, ethyl sulphamoyl, phenyl sulphamoyl, p-toluene sulphamoyl and the like), N,N-disubstituted sulphamoyl group. (for example N,N-dimethyl sulphamoyl, N-methyl-N-phenyl sulphamoyl, piperidino sulphamoyl, morpholino sulphamoyl and the like), carboxyl group, 1-10C alkoxycarbonyl group (for example methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, isobutoxy carbonyl, sec-butoxy carbonyl, tert butoxycarbonyl and the like), hydroxyl group, 1-10C alkoxy group, 2-10C alkenyloxy group, 3-7C cycloalkyl oxy group, aralkyloxy group, aryloxy group, mercapto group, 1-10C lower alkyl thio group, aralkyl thio group, arylthio group, sulfo group, cyano group, azido group, halogen atom, nitro group, nitroso group, oxo group and the like are nominated. As embodiment of

such substituent, for example, the one which is same it was denoted as the aforesaid hydrocarbon residue, heterocyclic group and substituent on amino group may be proposed.

In the aforesaid formula (I), as optionally substituted hydrocarbon residue represented by R1, as one preferred example, the group represented by formula -CH2-X3-Z1 [wherein, X3 denotes oxygen atom or the sulfur atom which may be oxidized, or -(CH2)x- (wherein, x denotes an integer of 0-5) and Z1 denotes optionally substituted hydrocarbon residue, optionally substituted heterocyclic group bonded to X3 at ring atom] may be proposed.

As the sulfur atom which may be oxidized represented by X3, thio group, sulfinyl group and sulphonyl group may be proposed. More particularly thio group is preferred.

Preferably X3 is -(CH2)x- (wherein, x is integer of 0-2, and more preferably x is 0).

As optionally substituted hydrocarbon residue represented by Z1, the one which is same as exemplified as optionally substituted hydrocarbon residue represented by the aforesaid R1 may be proposed.

As the optionally substituted heterocyclic group bonded to X3 by ring constituent atom represented by Z1, among the ones exemplified as optionally substituted heterocyclic groups represented by aforesaid R1, the same ones as the ones bonded to X3 by ring constituent atom may be proposed. Among these, aromatic 5 membered heterocyclic group including two or three heteroatom (for example oxygen atom, nitrogen atom, sulfur atom) is preferred.

In the aforesaid formula (I), as a preferred example of optionally substituted hydrocarbon residue represented by R1, the group represented by formula -(CH2)y-Z2 (wherein, y denotes an integer of 1-4 and Z2 denotes optionally substituted nitrogen-containing unsaturated heterocyclic group, being one bonded at the constituent nitrogen atom, respectively) may be proposed.

As the nitrogen containing unsaturated heterocyclic group of the said optionally substituted nitrogen containing unsaturated heterocyclic group, for example, unsaturated heterocycle containing at least one nitrogen atom as ring atom may be proposed. As embodiment of such unsaturated heterocyclic group, for example, 5 membered nitrogen-containing unsaturated heterocyclic group such as imidazol-1-yl, pyrazol-1-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, pyrrole-1-yl, tetrazol-1-yl, 2-pyrroline-1-yl, 3-pyrroline-1-yl, 2-imidazolin-1-yl, 2-pyrazoline-1-yl, 3-pyrazoline-1-yl and the like are preferred, and these may form condensed ring (for example

benzimidazol-1-yl, indol-1-yl, 1H-indazol-1-yl, benzotriazol-1-yl, benzotriazol-2-yl, iso indol-2-yl, 7-purinyl, 1H-pyrrolo (1,2-a) imidazol-1-yl, 1H-pyrrolo (1,2-b) (1,2,4) triazol-1-yl, 1,8a-dihydroimidazo (1,-2-a) pyridin-1-yl, 1,8a-dihydro (1,2,4) triazolo (1,5-a) pyridin-1-yl, 3,3a-dihydro (1,2,4) triazolo (1,5-a) pyrimidine-3-yl, 1,8a-dihydroimidazo (1,2-a) pyrimidine-1-yl, 1H-pyrazolo (4,3-d) oxazol-1-yl, 4H-imidazo [4,5-d] thiazol-4-yl and the like). Moreover, 6 membered nitrogen-containing unsaturated heterocyclic group such as 1,4-dihydropyridin-1-yl, 1,2-dihydropyridin-1-yl and the like are proposed, too, in addition to these 5 membered nitrogen-containing unsaturated heterocyclic groups.

As optionally substituted hydrocarbon residue represented by R1 the aforesaid formula (I), the group represented by formula -(CH2)Z-Z3 is proposed as preferred example. In the formula, it is propose that z denotes integer of 1-4 and Z3 denotes optionally substituted amino group represented formula -N(R5)(R6) [wherein, R5 and R6, which may be the same or different, denote hydrogen, optionally substituted hydrocarbon residue or optionally substituted heterocyclic group, or R5 and R6 may be bonded to each other forming the optionally substituted heterocyclic group].

As optionally substituted hydrocarbon residue or optionally substituted heterocyclic group represented by R5, R6, the same optionally substituted heterocyclic groups and optionally substituted hydrocarbon residues as exemplified with respect to respectively the aforesaid R1 may be respectively proposed.

R5 and R6 may bond together and form a ring, and as example of such -N(R5)(R6), for example 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidyl, piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, homopiperazin-1-yl, 1,2,4-triazol-1-yl, 1,3,4-triazol-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl, 1H-indazol-1-yl and the like may be proposed. These rings may have 1-3 substituents at the arbitrary substitutable position on ring thereof. Or as such substituent, the same as exemplified as substituent on optionally substituted hydrocarbon residue and optionally substituted heterocyclic group represented by R1 may be proposed. The said substituent may have further substituents, and as the said substituent which may have further substituents, the same ones as the optionally further substituted substituents in the substituents of the aforesaid hydrocarbon residue or heterocyclic group may be proposed.

Hydrocarbon residue and heterocyclic group represented by R5, R6 may contain 1-3 substituents at the arbitrary substitutable position the chain or ring. As such substituent, the one which is same as exemplified as substituent on optionally substituted hydrocarbon residue and optionally substituted

heterocyclic group represented by R1 may be proposed. The said substituent may have further substituents, and as the said substituent, same groups as the substituent which may have further substituent in the aforesaid hydrocarbon residue or substituent of heterocyclic group may be proposed.

In the aforesaid formula (II), as embodiment of the heterocyclic group which may be substituted represented by R4, the same as in an embodiment of the heterocyclic group which may be substituted represented by the aforesaid R1 may be proposed.

As embodiment of amino group which may be substituted represented by R4 the aforesaid formula (II), amino group which may be substituted represented by formula -N(R5)(R6) (wherein, R5 and R6 has same meaning as the aforesaid) may be proposed.

In the aforesaid formula (I) (II), as the sulfur atom which may be oxidised represented by X1 or X2, thio group, sulfinyl group and sulphonyl group are proposed. More particularly thio group is preferred.

In the aforesaid formula (I) (II), as the carboxyl group which might be esterified represented by G or G' (i) carboxyl group, (ii) one wherein 1-6C alkyl group was bonded to carboxyl group (namely, alkoxycarbonyl, for example methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxy carbonyl, isobutoxy carbonyl, sec-butoxycarbonyl, tert butoxycarbonyl, pentyloxy carbonyl, hexyl oxycarbonyl and the like), (iii) one wherein 3-6C alkenyl group is bonded to carboxyl group (namely, alkenyl oxycarbonyl, for example allyl oxycarbonyl, crotyl oxycarbonyl, 2-pentenyl oxycarbonyl, 3-hexenyl oxycarbonyl and the like) and (iv) the one wherein carbonyl group and aralkyloxy group are bonded (namely, aralkyl oxycarbonyl, for example benzyl oxycarbonyl, phenethyl oxycarbonyl and the like) may be proposed. In said aralkyl oxycarbonyl group, the aralkyl group denotes alkyl group having aryl group as substituent (arylalkyl group). As far as said aryl is concerned, for example, phenyl, naphthyl or the like may be proposed. These may contain substituent same as in the substituent which the heterocyclic group which may be substituted represented by the aforesaid R1 has. As said alkyl group, lower alkyl group of 1-6 C is preferred. For example as ideal example of said aralkyl group, benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl) methyl, (2-naphthyl) methyl or the like are proposed. Among these benzyl, phenethyl or the like is preferred.

In the aforesaid formula (I), the amidated carboxyl group represented by G is represented by -CON(R7)(R8) (wherein, R7 and R8 have same meaning as aforesaid R5 and R6).

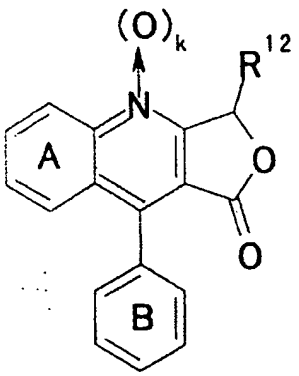
In the aforesaid formula (I), it is proposed that the acyl group represented by G denotes formyl, or a group represented by formula -CO-R9 (wherein, R9 denotes a 1-10C alkyl group or 6-14C aryl group or 2-10 C alkenyl group). As embodiment of 1-10C alkyl group represented by R9, 2-10 C alkenyl group or 6-14C aryl group, the same ones respectively as aforesaid may be proposed.

When G is hydroxyalkyl group, as alkyl group of such hydroxyalkyl group, 1-8C alkyl group from among examples of hydrocarbon residue represented by the aforesaid R1 is proposed. Said hydroxyalkyl group is represented preferably by -CH2OH or CH(OH)-R10 (for R10, 1-7C alkyl group is proposed from those shown as examples of the hydrocarbon residue represented by the aforesaid R1). R10 in this formula is preferably methyl, ethyl or the like.

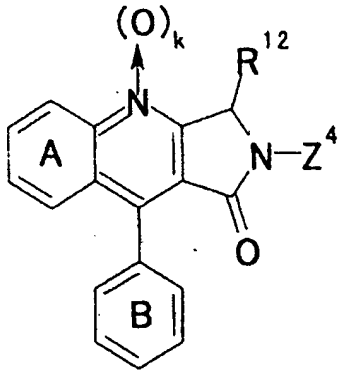
When G is protected hydroxyalkyl group, the protected hydroxy in this group is represented by formula -CH2OCOR11 or CH(OCOR12)-R10 (R10 has the same meaning as the aforesaid, and R11 and R12 each independently denote optionally substituted alkyl group, aralkyl group or aryl group) . As alkyl group represented by R11 and R12, 1-6C alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, terl-butyl and the like may be proposed. As aralkyl group represented by R11 and R12, 1-4C alkyl groups having 6-14C aryl group as substituent (6-10C aryl – alkyl group) are denoted. As said 6-10C aryl group, for example, phenyl, naphthyl or the like may be proposed, and as said aralkyl group, for example benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl) methyl, (2-naphthyl) methyl and the like may be proposed. As 6-10C aryl represented by R11 and R12, for example, phenyl, naphthyl and the like may be proposed.

When G' is halogen atom, as such halogen atom, chlorine, bromine, iodine, fluorine are nominated, preferably chlorine or bromine

In the aforesaid formula (I), when Y is C-G, R1 and G may bond together forming 5 membered ring. Such structure is represented by following formula (III) and (IV).



[III]



[IV]

(wherein, R12 denotes hydrogen, optionally substituted hydrocarbon residue or the heterocyclic group which may be substituted, Z4 denotes optionally substituted hydrocarbon residue, optionally substituted heterocyclic group or optionally substituted amino group, and other symbol has same meaning as the aforesaid).

In (III) and (IV), as the optionally substituted hydrocarbon residue and optionally substituted heterocyclic residue represented by R12 and Z4, the same ones as exemplified as the aforesaid R1 may be proposed. As embodiment of amino group which may be substituted represented by Z4, the same as the amino group which may be substituted represented by the aforesaid Z3 may be proposed.

Moreover, 5-7 membered ring may be formed by bonding together of R2 and R3 on adjacent carbon atom on thiophene ring, (namely, vinylene group). As 5-7 membered heterocyclic group formed by bonding of R2 and R3, (i)5-7C alicyclic hydrocarbon group or (ii) 5-7 membered ring containing 1 nitrogen atom optionally substituted by optionally substituted 1-10C alkyl (preferably 1-4C alkyl) or 1-4 oxygen atoms, 1-4 optionally oxidised sulfur atoms may be proposed.

The R2 and R3 part of said 5-7 membered ring is represented by -R2-R3-, and as embodiments for example, -(CH2)3-, -(CH2)4-, -(CH2)5-, -CH2-N(M)-CH2-CH2-, -CH=N-CH2-CH2-, -CH=N-CH=CH-, -N=CH-CH=CH-, -CH-=CH-N=CH-, -N(M)-CH2-CH2-CH2-, -CH2-CH2-N(M)-CH2-, -CH2-S-CH2-CH2-, -CH2-SO-CH2-CH2-, -CH2-SO2-CH2-CH2-, -CH2-O-CH2-CH2- and the like may be proposed. Preferably-CH2-N(M)-CH2-CH2-(M is methyl, ethyl, propyl, benzyl and the like), -CH=N-CH2-CH2-, -CH=N-CH=CH width may be proposed.

M in the aforesaid formula (I) denotes a hydrogen atom, optionally substituted hydrocarbon residue, optionally substituted acyl group, optionally substituted carbamoyl group, optionally substituted thiocarbamoyl group or optionally substituted sulphonyl group.

As optionally substituted hydrocarbon residue represented by M, same group as optionally substituted hydrocarbon residue represented by R1 may be proposed. For example as optionally substituted hydrocarbon residue represented by M, optionally substituted 1-4C alkyl group (for example, methyl, ethyl, isopropyl, propyl, butyl, benzyl, phenethyl, 2-, 3- or 4-pyridylmethyl, phenyl group optionally substituted by 1-4C alkyl group and the like) may be proposed.

As the acyl group which may be substituted represented by M, the acyl group which is same acyl group as ones exemplified as acyl group of substituent of optionally substituted hydrocarbon residue and heterocyclic group represented by the aforesaid R1 may be proposed.

As the carbamoyl group which may be substituted represented by M, one denoted by R13NHCO- is proposed (R13 has the same meaning as aforesaid R1).

As the thiocarbamoyl group which may be substituted represented by M, one denoted by RINHCS- is proposed (R13 has the same meaning the aforesaid R1).

As the sulphonyl group which may be substituted represented by M, one denoted by RSO2- is proposed (R13 has the same meaning the aforesaid R1).

As optionally substituted hydrocarbon residue represented by M, 1-10C alkyl group (more particularly 1-3C (for example, methyl, ethyl, propyl isopropyl and the like) or 1-4C alkyl group optionally substituted by phenyl group is preferred.

The phenyl group as substituent on chain of optionally substituted 1-4C alkyl group represented by M may have 1 or more, preferably 1-3, further substituents at arbitrary substitutable positions, and as the said substituents

1-10C lower alkyl group, 2-10C lower alkenyl group, 2-10C lower alkynyl group, 3-7C cycloalkyl group, 3-7C cycloalkenyl group, 4-7C cycloalkadienyl group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, aralkyl group. (for example aryl 1-6C alkyl group and the like),

amino group, N-mono substituted amino group, N,N-disubstituted amino group, amidino group, acyl group, carbamoyl group, N-mono substituted carbamoyl group (for example, methylcarbamoyl, ethyl carbamoyl, phenylcarbamoyl and the like), N,N-disubstituted carbamoyl group (for example N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, piperidino carbamoyl, morpholino carbamoyl and the like), sulphamoyl group, N-mono substituted sulphamoyl group (for example methyl sulphamoyl, ethyl sulphamoyl, phenyl sulphamoyl, p-toluene sulphamoyl and the like). N,N-disubstituted sulphamoyl group (for example N,N-dimethyl sulphamoyl, N-methyl-N-phenyl sulphamoyl, piperidino sulphamoyl, morpholino sulphamoyl and the like), carboxyl group, 1-10C lower alkoxycarbonyl group (for example methoxycarbonyl, ethoxycarbonyl, isopropoxy carbonyl, sec-butoxy carbonyl, isobutoxycarbonyl, tert-butoxy carbonyl and the like), hydroxyl group, 1-10C lower alkoxy group, 2-10C lower alkenyloxy group, 3-7C cycloalkyl oxy group, aralkyloxy group, aryloxy group, mercapto group, 1-10C lower alkyl thio group, aralkyl thio group, arylthio group, sulfo group, cyano group, azido group, nitro group, nitroso group, oxo group, halogen and the like may be proposed, like the ones shown as substituents of the said R1.

As optionally substituted hydrocarbon residue represented by M, phenyl 1-3C alkyl (for example benzyl, phenethyl, 4-methoxybenzyl or the like) is more preferred.

As optionally substituted 5-7 membered ring (-R2-R3-) formed by bonding R2 and R3, -CH2-N(CH3)-CH2-CH2-, -CH2-N(-CH2-C6H5)-CH2-CH2-, -CH2-N(-CH2-B-OCH3)-CH2-CH2-(B denotes p-phenylene group), -CH2-NH-CH2-CH2- or the like are preferred.

As particularly preferred R2 and R3, it may be proposed that R2 and R3 are both methyl group, or R2 and R3 bonded together as -R2-R3- are -CH2-N(M)-CH2-CH2- (M is hydrogen atom, 1-3C alkyl or benzyl) to form the 6 membered-ring containing nitrogen atom.

In the said formula (I), ring A and ring B may have substituent, and as example of such substituent, halogen atom, nitro group, optionally substituted 1-10C alkyl group, optionally substituted 2-10C alkenyl group, optionally substituted 2-10C alkynyl group, optionally substituted hydroxy group, optionally substituted thiol group, optionally substituted amino group, optionally substituted acyl group (for example 1-10C alkanoyl group, 2-10C alkenoyl group, 2-10C alkynoyl group), optionally esterified carboxyl group or the optionally substituted aromatic ring group are used.

As example of the halogen which was shown as substituent of ring A and ring B, fluorine, chlorine, bromine and iodine are proposed. More particularly fluorine and chlorine are preferred.

As optionally substituted 1-10C alkyl group as substituent of ring A and ring B, it may be any of straight chain alkyl of 1-10C, branched alkyl of 3-10C, cyclic alkyl of 3-10 C, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like are nominated. These 1-10C alkyl group, 2-10C alkenyl group, 2-10C alkynyl group may have 1-3 substituents same as in substituent described above in hydrocarbon residue and heterocyclic group represented by R or Z1, in the arbitrary substitutable position.

As the optionally substituted hydroxy group shown as substituent of Ring A and Ring B, the hydroxy group which is (i) hydroxy group, and (ii) hydroxy group having a suitable substituent on the hydroxy group, particularly one used as protecting group of hydroxy group (for example alkoxy, alkenyloxy, alkynyl oxy, aralkyloxy, acyl oxy, aryloxy or the like) may be proposed.

As said alkoxy, 1-10C alkoxy (for example methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso butoxy, sec-butoxy, tert butoxy, pentyloxy, isopentyloxy, neopentyl oxy, hexyloxy, heptyl oxy, nonyl oxy, cyclobutyl oxy, cyclopentyl oxy, cyclohexyl oxy and the like) is preferred.

As said alkenyloxy, 2-10C alkenyloxy (for example allyl oxy, crotyl oxy, 2-pentenyl oxy, 3-hexenyl oxy, 2-cyclopentenyl methoxy, 2-cyclohexenyl methoxy and the like) may be proposed.

As said alkynyl oxy, 2-10C alkynyl oxy (for example, propynyl oxy and the like) may be proposed.

As said aralkyloxy, for example phenyl-C1-4 alkoxy (for example, benzyloxy, phenethyl oxy and the like) may be proposed.

As said acyl oxy, 2-4C alkanoyloxy (for example, acetyl oxy, propionyloxy, butyryl oxy, isobutyryl oxy and the like) are preferred.

As aryloxy, phenoxy, 4-chlorophenoxy and the like may be proposed.

As the optionally substituted thiol group as substituent of ring A and ring B, (i) thiol group and (ii) thiol group having suitable substituent, particularly the one used as protecting group of thiol group, for example alkylthio, alkenyl thio, alkynyl thio, aralkyl thio, acylthio, arylthio and the like, may be proposed.

As said alkylthio, 1-10C alkylthio (for example methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutyl thio, sec-butylthio, tert-butylthio, pentyl thio, isopentyl thio, neopentyl thio, hexyl thio, heptyl thio, nonyl thio, cyclobutyl thio, cyclopentyl thio, cyclohexyl thio and the like) is preferred.

As said alkenyl thio, 2-10C alkenyl thio (for example allyl thio, crotyl thio, 2-pentenyl thio, 3-hexenyl thio, 2-cyclopentenyl methylthio, 2-cyclohexenyl methylthio and the like) may be proposed.

As said alkynyl thio, 2-10C alkynyl thio (for example ethinyl thio, 2-propynyl thio and the like) may be proposed.

As said aralkyl thio, for example phenyl-C1-4 alkylthio (for example, benzylthio, phenethyl thio and the like) may be proposed.

As said acylthio, 2-4C alkanoyl thio (for example, acetylthio, propionyl thio, butyryl thio, isobutyryl thio and the like) are preferred.

As said arylthio, phenylthio, 4-chlorophenylthio and the like may be proposed.

As optionally substituted amino group shown as substituent of ring A and ring B, (i) amino group and (ii) amino group having 1 or 2 substituents of 1-10C alkyl, 2-10 C alkenyl, 2-10 C alkynyl, 1-10 C acyl group, 6-12C aromatic group or heterocyclic group (for example methylamino, dimethylamino, ethylamino, diethylamino, dibutyl amino, diallyl amino, cyclohexyl amino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionyl amino, benzoylamino, nicotinoyl amino and the like) may be proposed.

As the optionally substituted acyl group shown as substituent of ring A and ring B, (i) formyl and (ii) the one wherein 1-10C alkyl, 2-10 C alkenyl, 2-10 C alkynyl or 6-12C aromatic group are bonded to carbonyl group may be proposed (for example acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutane carbonyl, cyclopentane carbonyl, cyclohexane carbonyl, cycloheptane carbonyl, crotonyl, 2-cyclohexene carbonyl, benzoyl, nicotinoyl and the like).

As the optionally esterified carboxy shown as substituent of ring A and ring B, (i) carboxyl group, (ii) one wherein 1-6C alkyl group is bonded to carboxyl group (namely, alkoxycarbonyl, for example

methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxy carbonyl, in butoxycarbonyl, sec-butoxy carbonyl, tert butoxycarbonyl, pentyl oxycarbonyl, hexyl oxycarbonyl and the like), (iii) one wherein 3-6C alkenyl group is bonded to carboxyl group (namely, alkenyl oxycarbonyl, for example allyl oxycarbonyl, crotyl oxycarbonyl, 2-pentenyl oxycarbonyl, 3-hexenyl oxycarbonyl and the like) and (iv) the one wherein carbonyl group and aralkyloxy group are bonded (namely, aralkyl oxycarbonyl, for example benzyl oxycarbonyl, phenethyl oxycarbonyl and the like) may be proposed.

As the optionally substituted aromatic ring group shown as substituent of ring A and Ring B, 6-14C aromatic hydrocarbon residue (for example, phenyl, naphthyl, anthryl and the like) and heteroaromatic residue (for example, pyridyl, furyl, thienyl, imidazolyl, thiazolyl and the like) may be proposed.

Such substituents of Ring A and Ring B may be substituted at any substitutable position on each ring, and there may be 1-4 the same or different substituents on each of ring A and ring B. When substituent son ring A or ring B are mutually adjacent, they may bond together forming a ring, shown as -(CH2)t- or -O-(CH2)l-O- (wherein, t is integer of 3-5, and 1 denotes an integer of 1-3), and such ring includes 5-7 membered ring formed with carbon atom of benzene ring.

Preferably ring A is substituted by at least one alkoxy group (preferably 1-3C alkoxy group), more preferably at least one methoxy. More preferably ring A is substituted by 2 same or different alkoxy group (preferably 1-3C alkoxy group), preferably methoxy. As embodiments, for example, the case wherein Ring A is substituted by two methoxy groups at 6-position and 7-position of quinoline ring or quinazoline ring is particularly preferred.

Preferably ring B is substituted by at least one alkoxy group (preferably 1-3C alkoxy group), more preferably at least one methoxy or isopropoxy. More preferably ring B is substituted by 2 same or different alkoxy group (preferably 1-3C alkoxy group) . As embodiments, for example, the case wherein ring B is substituted by methoxy group or isopropoxy group at 3 position and is substituted by methoxy group at 4 position is particularly preferred.

Ring D of compound the aforesaid formula (II) is substituted by at least one alkoxy group (preferably 1-3C alkoxy group), more preferably at least one methoxy or isopropoxy. More preferably ring D is substituted by one alkoxy group (preferably 1-3C alkoxy group).

As embodiments, for example, the case that ring D is substituted by the methoxy group at 4 position is particularly preferred.

In compound represented with the aforesaid formula (I), as the one particularly preferred, the compound wherein Y is C-G" (G" denotes a carboxyl group which may be esterified) and R1 is 1-4C alkyl group substituted by nitrogen-containing unsaturated heterocyclic group (wherein, the constituent nitrogen atom of the nitrogen-containing unsaturated heterocyclic group is bonded to said 1-4C alkyl group), and n of 0 is nominated.

In compound represented by the aforesaid formula (II), as the one particularly preferred, the compound wherein R2 and R3 bond together, forming a 5-7 membered ring which may be substituted is formed, and as embodiment, R2 and R3, by bonding together with the adjacent hydrogen atoms (namely vinylene) of the thiophene ring form 5-7 membered ring, and G' of C-G' represented by W shows halogen atom may be proposed.
For example 3-chloro-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine,
3-chloro-4-(3, 4-dimethoxy phenyl)-5,6,7,8-tetrahydro-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine,
3-chloro-4-(4-ethoxyphenyl)-5,6,7,8-tetrahydro-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine.
3-bromo-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine.
7-acetyl-3-chloro-5,6,7,8-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine,
7-acetyl-3-chloro-5,6,7,8-tetrahydro-4-(4-hydroxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine,
7-acetyl-3-chloro-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine,
7-acetyl-3-chloro-4-(4-ethoxyphenyl)-5,6,7,8-tetrahydro-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine,
7-acetyl-3-chloro-4-(3, 4-dimethoxy phenyl)-5,6,7,8-tetrahydro-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine, or salts thereof may be proposed.

As salt of quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative that can be used in this invention, pharmacologically acceptable salt is preferred, and salt of for example

inorganic base, salt of organic base, salt of inorganic acid, salt of organic acid, salt of basic or acidic amino acid and the like may be proposed.

As ideal example of salt of said inorganic base, alkali metal salt (for example, sodium salt, potassium salt and the like), alkaline earth metal salt (for example, calcium salt, magnesium salt and the like), aluminium salt, ammonium salt and the like may be proposed.

As ideal example of salt of said organic base, for example salt such as trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N, N'-dibenzylethylenediamine or the like may be proposed.

As ideal example of salt of inorganic acid, salt such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid or the like may be proposed.

As ideal example of salt of organic acid, salt such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or the like may be proposed.

As ideal example of salt of basic amino acid, salt such as arginine, lysine, ornithine or the like may be proposed. As ideal example of salt of acidic amino acid, salt such as aspartic acid, glutamic acid or the like may be proposed.

Of these salts, sodium salt, potassium salt are most preferred.

Moreover, quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative or salts thereof may be hydrate in this invention.

In this invention, for example, quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative can be readily produced according to a process for production reported in Kokai 6-306052 (EP-A-567107), Kokai 7-118266 (EP-A-608870), Kokai 7-69890 (EP-A-634169), Kokai 8-53419 (EP-A-686630), Kokai 8-225531 (WO95/24394), Kokai 8-225577 (WO96/14319), Kokai 10-36374 and 10-59977 (WO97/40050) or method based on these.

As gel-forming substance contained in sustained-release oral preparation of this invention, water-soluble polymer compound is ideal. As water-soluble polymer compound, compounds having viscosity of preferably about 2-36000 mPa_S, more preferably have about 2-4000 mPa_S, even more

preferably 2-1500 mPa_S (2%(W/W) aqueous solution based on dried material is measured under condition of 20° C+/-0.1° C) are preferred. As water-soluble polymer compounds, for example, cellulose derivative, polyvinyl system polymer or polyvalent alcohol and the like are nominated.

As far as said cellulosic derivatives are concerned, for example, hydroxypropyl methyl cellulose [example, Grade TC-5EW (viscosity: 2-4 mPa_S), TC-5MW (viscosity: 3-6 mPa_S), TC-5R (viscosity: 4-8 mPa_S), TC-5S (viscosity: 12-18 mPa_S), 60SH-50 (viscosity: 40-60 mPa_S), 65SH-50 (viscosity: 40-60 mPa_S), 65SH-400 (viscosity: 320-480 mPa_S), 90-SH400 (viscosity: 320-480 mPa_S), 90SH-30000F (viscosity: 24000-36000 mPa_S)], hydroxypropylcellulose, low degree of substitution hydroxypropylcellulose, methyl cellulose, carboxymethylcellulose, crosscarmellose sodium, carmellose calcium and the like may be proposed.

As said polyvinyl system polymer, for example, polyvinylpyrrolidone, carboxyvinyl polymer and the like may be proposed.

The said polyvalent alcohol in this specification, refers to a polyvalent alcohol which is solid at 25° C, and for example polyethyleneglycol (preferably polyethyleneglycol having average molecular weight of about 8000-70000), polypropylene alcohol, polyglycerol and the like may be proposed.

As said gel-forming substance, preferably cellulose derivatives, more preferably hydroxypropyl methyl cellulose or hydroxypropylcellulose, even more preferably hydroxypropyl methyl cellulose are used.

As disintegration aid contained in the sustained-release oral preparation of this invention, saccharides are preferred, and as said saccharides, for example sugar alcohol (for example erythritol, sorbitol, mannitol, maltitol, xylitol, reduced starch sugar, reduced palatinose and the like), monosaccharide (for example, glucose, mannose, xylose, galactose, talose and the like), polysaccharides (for example maltose, lactose, sucrose or the like) and the like may be proposed.

As said saccharide, more preferably, erythritol or sorbitol is used.

Preferably (1) quinoline or quinazoline derivative or thienopyridine or thienopyrimidine derivative : (2) gel-forming substance are mixed in weight ratio of about 1 : about 0.1-100, and used. As the said proportion, about 1 : about 0.1-50 is preferred, and about 1 : about 0.2-20 are furthermore preferred.

When (3) disintegration aid is formulated in the oral sustained release preparation of this invention furthermore, preferably, Preferably (1) quinoline or quinazoline derivative or thienopyridine or thienopyrimidine derivative : (2) gel-forming substance : (3) disintegration aid are used in quantities comprising about 1 : about 0.1-50 : about 0.01-50, more preferably, quantities comprising about 1 : about 0.1-50 : about 0.05-30, and most ideally about 1 : about 0.2-20 : about 0.1-20 by weight ratio.

In oral sustained release preparation of this invention, the gel-forming substance is formulated preferably in amount of about 10 wt.% or more with respect to the whole preparation, more preferably about 10-99.9 wt.%, more preferably about 20-90 wt.%, and in particular preferably about 15-95 wt.%.

When the disintegration aid is further formulated in the oral preparation of this invention, the disintegration aid is formulated preferably in amount of about 1 wt.% or more with respect to the whole preparation, more preferably about 1-90 wt.%, ever more preferably about 3-70 wt.%, in particular preferably about 5-50 wt.% and ideally about 5-23 wt.%.

The sustained-release oral preparation of this invention is for example formed into tablet, granule or the like. Even encapsulated formulation including granule is good. In such cases, the gel-forming substance and disintegration aid may be formulated in the inside of the preparation or may be coated on the surface of the preparation.

The controlled-release oral tablet can be obtained by mixing the effective ingredient and other preparation additives and thereafter directly pressure forming (compression) or by temporarily pressure forming then granulating and thereafter pressure forming (compression). Moreover, the mixture including effective ingredient and excipient is granulated, thereafter graded powder is formed, then, other preparation materials are mixed, and it may be tabletted.

The aforesaid graded powder can be prepared using binding agent by conventional method and process such as wet granulation method, dry granulation method or the like. The preferred graded powder is obtained by wet granulation method, for example stirring granulation method, fluidized bed granulation method or the like. For example, the average particle diameter of the graded powder is about 0.1-2000 μm, more preferably about approx 10-500 μm.

The tablet of this invention can be formulated pharmaceutically according to generally used well-known process. For example, pharmacologically acceptable carrier is formulated to the drug which is used in this invention, it can be moulded into tablet.

As pharmacologically acceptable carrier, various organic or inorganic support substances conventionally used as the preparation material can be used, and excipient, lubricant, binding agent, disintegrating agent or the like are formulated. Moreover, preparation additives such as preservatives, anti-oxidant, colorant, sweetener or the like can be used in accordance with requirements. Moreover, when these pharmacologically acceptable carriers are compounds having action of the aforesaid gel-forming substance or disintegration aid, it is assumes that the quantity formulated of said compound is added to the compounding ratio and formulated proportion of the oral preparation of this invention, and it is calculated.

As ideal example of excipient, for example, lactose, refined sugar, D-mannitol, erythritol, starch, crystalline cellulose, light anhydrous silicic acid and the like may be proposed.

As ideal example of lubricant, for example, magnesium stearate, calcium stearate, talc, colloidal silica and the like may be proposed.

As ideal example of binding agent, for example, crystalline cellulose, pregelatinised starch, partially pregelatinised starch, refined sugar, D-mannitol, trehalose, dextrin, hydroxypropylcellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone and the like may be proposed. Preferably crystalline cellulose is used.

As ideal example of disintegrating agent, for example starch, carboxymethylcellulose, carboxymethylcellulose calcium, crosscarmellose sodium, carboxymethyl starch sodium, low degree of substitution hydroxypropylcellulose and the like may be proposed.

The oral administration preparation can be formed by coating by a well-known process for the purpose of masking the taste, imparting enteric solubility or sustained release in accordance with requirements.

As coating agent thereof, for example, hydroxypropyl methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxymethyl cellulose

acetate succinate, Eudragit (methacrylic acid / acrylic acid copolymer made by Rohm company, Germany) may be proposed.

As ideal example of preservatives, for example parahydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like may be proposed.

As ideal example of anti-oxidant, for example sulfite ascorbic acid and the like may be proposed. As colorant, titanium oxide, 32 iron oxide (red iron oxide), food color and the like may be proposed. As sweetener aspartame, saccharin sodium, glycyrrhizin dipotassium, Stevia and the like may be proposed.

Moreover, for example, when the sustained release oral preparation of this invention is produced as granule, (1) quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative, (2) gel-forming substance and furthermore (3) disintegration aid in accordance with requirements are mixed, thereafter, using a binding liquid dissolved in a suitable solvent, kneading, granulation, drying and grading are carried out with conventional procedures and the granules are formed. Capsule is filled up with this granule, and encapsulated formulation can be formed.

In the sustained-release oral preparation of this invention, the release period of drug can be suitably regulated by the quantity formulated of gel-forming substance or the like or quantities formulated of gel-forming substance and the disintegration aid. Usually, the sustained-release oral preparation of this invention denotes a sustained release time of about 1-48 hour, preferably about 1-24 hour, more preferably about 3-24 hour.

In accordance with this invention, for example, when the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative or salts thereof has antiinflammatory action, and also anti arthritis action, the sustained-release oral preparation of this invention can be used as therapeutic or preventive agent or the like of all kinds of arthritis presenting inflammation symptom of joints. As said arthritis, for example, chronic rheumatism and the like may be proposed.

Moreover, for example, when the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative or salts thereof has antirheumatic action, the sustained-release oral preparation of this invention can be used as therapeutic or preventive agent of rheumatism and the like.

Moreover, for example, when the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative or salts thereof has bone resorption inhibitory action, the sustained-release oral

preparation of this invention can be used as therapeutic or preventive agent of bone destruction bone resorption depressant accompanying arthritis, preventive or therapeutic agent or the like of osteoporosis or the like.

Moreover, for example, when the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative or salts thereof has immunologic cytokine production inhibitory action, the sustained-release oral preparation of this invention can be used as preventive or therapeutic agent of diseases thought to involve immunity and/or preventive or therapeutic agent of graft rejection after organ transplantation or the like.

When the quinoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative or salts thereof has an immunomodulation action or action to inhibit production of immunologic cytokine (for example interleukin-2 (IL-2), interferon-gamma (IFN-gamma) and the like), the sustained-release oral preparation of this invention can be used as therapeutic or preventive agent or the like of diseases thought to involve immunity including autoimmune disease.

As such target diseases, for example systemic erythmadosus, inflammatory enteric disease (ulcerative colitis, Crohn's disease), multiple sclerosis, psoriasis, chronic hapatitis, bladder cancer, breast cancer, the amount of uterus cancer parts, chronic lymphatic leukocyte, chronic myelogenic leukemia, large intestine cancer, colon cancer, rectum cancer, Helicobacter pylori infection, Hodgkin's disease, insulin-dependent diabetes mellitus, malignant melanoma, multiple myeloma, non Hodgkin's lymphoma, non small cell lung cancer, ovary cancer, peptic ulcer, prostate gland cancer, septicemia shock, tuberculosis, infecundity, arteriosclerosis, Behchet's disease, asthma, atopic dermatitis, nephritis, systemic fungal infection, acute bacteria meningitis, acute cardiac infarction, acute pancreatitis, acute viral encephalitis, adult tachypnea syndrome, bacteria pneumonia, chronic pancreatitis, herpes simplex virus infection, varicella-herpes zoster viral infection, AIDS, human papillomavirus infection, influenza, invasiveness Staphylococcus infection, peripheral vascular disease, septicemia, interstitial liver disease, regional ileitis and the like may be proposed. More particularly the sustained-release oral preparation of this invention is used as therapeutic or preventive agent or the like of systemic erythematosus, chronic hepatitis, interstitial liver disease asthma, psoriasis, ulcerative colitis, Crohn's disease, terminal ileitis or multiple sclerosis or the like.

The oral preparation of this invention has low toxicity, therefore, it can be used safely with respect to mammalian organisms (for example human, cow, horse, pig, dog, cat, mouse, rat, rabbit and the like).

The sustained-release oral preparation of this invention releases a certain amount of drug over a long period of time, and a stable drug efficacy is obtained, therefore it can be used as a preparation of high indication.

The dose of sustained-release oral preparation of this invention differs depending on the type of quinazoline or quinazoline derivative or thienopyridine or thieno pyrimidine derivative contained, the content, pharmaceutical form, administration subject animal or the like, however, it is effective doses of these drugs are used and it is administered about 10-500 mg per adult (as 50 kg in weight) per person divided by 1-3 times per day.

Below Examples, Reference Examples and Test Examples are proposed, and this invention is described in greater detail. However, this invention is not restricted to these.

Compound A used in the following Examples 1-16 and Reference Example 1 was ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-yl methyl) quinoline-3-carboxylate, and the compound produced by process of description in Kokai 7-118266 or Kokai 8-67679 was used.

Example 1

Compound A 400g, hydroxypropyl methyl cellulose (made by grade TC-5MW, Shin-Etsu Chemicals Co. Ltd.) 324 g and erythritol 40 g were introduced into transfer-fluidized bed granulation machine (MP-10 made by Powrex Co.) and, under conditions of gas supply temperature 65° C, spray velocity 19g/min, fluidized bed granulation was carried out while spraying 10 wt.% hydroxypropyl methyl cellulose 400 g. After granulation, thereafter, it was dried to product temperature 32° C, and granulation powder 600 g were weighed, and crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 15 g, light anhydrous silicic acid (grade Silysia 320, made by YKF Ltd.) 6 g, magnesium stearate 6 g were added, and it was mixed. Using tablet machine (Correct 19K AWC, made by KIKUSUI SEISAKUSHO LTD.), this mixture was formed into tablets using 10 mm phi corners-cut punch (compression pressure 0.2ton/tablet). The tablet was formed into graded powder using a Power Mill (P-3, Showa Giken Co. Ltd) with punching size 1.5 mm phi. Sing the tablet machine (Correct 19K AWC, made by KIKUSUI SEISAKUSHO LTD.) once again the obtained graded powder was formed into tablet of 429 mg with of 10 mm phi corners-cut punch (compression pressure 1.0 ton/ tablet).

Example 2

Compound A 400g, hydroxypropyl methyl cellulose (grade TC-5EW, made by Shin-Etsu Chemicals Co. Ltd.) 324 g were introduced into transfer fluidized bed granulation machine (MP-10 made by

Powrex Co.) and fluidized bed granulation was done while spraying 10 wt.% hydroxypropyl methyl cellulose 400 g of under conditions of gas supply temperature 60° C spray velocity 19g/min. After granulation, it was dried to product temperature 33° C, and graded powder 600 g were weighed, and crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 15 g, light anhydrous silicic acid (grade Silysia 320, made by YKF Ltd.) 6.1 g, magnesium stearate 6.1 g were added, and it was mixed. Using tablet machine (Correct 19K AWC, made by KIKUSUI SEISAKUSHO LTD.), this mixture was formed into tablet by tablet of 10 mm phi corner-cut punch (compression pressure about 0.2 ton/ tablet). The tablet was formed into graded powder using a Power Mill (P-3, Showa Giken Co. Ltd) with punching size 1.5 mm phi. Sing the tablet machine (Correct 19K AWC, made by KIKUSUI SEISAKUSHO LTD.) once again the obtained graded powder was formed into tablet of 429 mg with of 10 mm phi corners-cut punch (compression pressure 1.0 ton/ tablet).

Examples 3-6

Compound A 2g, hydroxypropyl methyl cellulose 1.9 g [grade TC-5EW (Example 3), grade TC-5MW (Example 4), grade TC-5R (Example 5), grade TC-5S (Example 6)], crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 100 mg were weighed, and it was mixed with mortar. This mixed powder 400 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Examples 7-8

Compound A 2g, hydroxypropyl methyl cellulose 925 mg [grade TC-5EW (Example 7), grade TC-5MW (Example 8)], crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 75 mg were weighed, and it was mixed with mortar. This mixed powder 300 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Example 9

Compound A 2g, hydroxypropyl methyl cellulose 630 mg (grade TC-5MW), crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 70 mg were weighed, and it was mixed with mortar. This mixed powder 270 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Example 10

Compound A 2g, hydroxypropyl methyl cellulose 3.85 g (grade TC-5EW), crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 150 mg were weighed, and it was mixed with mortar. This mixed powder 600 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Example 11

Compound A 2g, hydroxypropyl methyl cellulose 1.8 g (grade TC-5EW), crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 100 mg, erythritol 1 g, light anhydrous silicic acid (grade Silysia 320, made by YKF Ltd.) 50 mg, magnesium stearate 50 mg were weighed, and it was mixed with mortar. This mixed powder 500 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Example 12

Compound A 2g, hydroxypropyl methyl cellulose 1.8 g (grade TC-5EW), crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 100 mg, sorbitol 1 g, light anhydrous silicic acid (grade Silysia 320, made by YKF Ltd.) 50 mg, magnesium stearate 50 mg were weighed, and it was mixed with mortar. This mixed powder 500 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Examples 13-16

Compound A2g, hydroxypropyl methyl cellulose 1.42 g (grade TC-5MW), crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 100 mg, light anhydrous silicic acid (grade Silysia 320, made by YKF Ltd.) 40 mg, magnesium stearate 40 mg, additive 400 mg [lactose (Example 13), crosscarmellose sodium (AcDiSol made by Asahi Chemical Industry) (Example 14) low degree of substitution hydroxypropylcellulose (grade LH-31) (Example 15) carmellose calcium (grade ECG-505) (Example 16)] were weighed, and it was mixed with mortar. This mixed powder 400 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2 with 10 mm phi corner-cut punch, and tablets were produced.

Reference Example 1

Compound A 478.9g, lactose 218.5 g, corn starch 127.9 g were introduced into transfer fluidized bed granulation machine (MP-10 made by Powrex company) and fluidized bed granulation was done while

spraying 6 wt.% hydroxypropylcellulose aqueous solution 520 g under conditions of supply air temperature of 70° C, spray velocity 10 g/min. After granulation, it was dried to product temperature 45° C, and this dried material was pulverised with a Power Mill (P-3 made by Showa Giken Co. Ltd, punching size 1.2 mm phi), and graded powder was produced. Thereafter, using this graded powder 853 g, crosscarmellose sodium (AcDiSol made by Asahi Chemical Industry Co. Ltd.) 45.5 g, magnesium stearate 2.7 g, polyethyleneglycol 6000 (Sanyo Chemical Co.) 9.1 g were mixed. With this mixed powder, using tablet machine (Comect 19K AWC, made by KIKUSUI SEISAKUSHO LTD.) tablet of 190 mg was produced per tablet by 7 mm phi corner-cut punch (compression pressure 1.0 ton/cm2).

Experimental Example 1.

The disintegration time of the tablets produced in Examples 4, 13, 14, 15, 16 was investigated according to Pharmacopeia of Japan disintegration test method, using disintegration test machine (Tomiyama industry Co. Ltd.) without disc, and as a result, that of tablet obtained in Example 4 was 160 minutes, that of tablet of Example 13 was 130 minutes, that of of tablet of Example 14 was , 90-120 minutes, that of tablet of Example 15 was 140 minutes, and that of tablet of Example 16 was 130 minutes.

Experimental Example 2.

One tablet each obtained in Examples 1-12 and Reference Example 1 was accurately weight (WT), and using 0.6 % sodium lauryl sulfate (SLS) aqueous solution 900 ml, the test was carried out at 50 rpm by paddle method. The sampling was carried out with time by 2 ml, the sample was filtered with membrane filter of 0.45 μm, and 1 ml was accurately sampled, and was diluted with accurately measured mobile phase 8 ml, and sample solution was made. Separately, compound A 20 mg was measured precisely (WS), mobile phase were added, and made up to 100 ml precisely. This liquid 1 ml was sampled precisely, was diluted with accurately measured mobile phase 8 ml, and it was made as standard solution. The sample solution and standard solution 10 ml were measured by liquid chromatography. Peak area of compound A was assigned as QT and QS, and elution rate was calculated using the following equation.

Elution rate (%) = QT/QS x 0.9 x WS x content x theoretical formulation /WT/20

The results are shown in [table 1] and [table 2].

[Table 1]

Tablet of Reference Example 1,

Time (hr)	0	0.088	0.25	0.5	0.75		
Elution rate (%)	0	16.6	41.9	78.6	101.		

Tablet of Example 1,

Time (hr)	0	1	2	3	4	5	6
Elution rate (%)	0	9.8	27	45.2	61.7	75.1	84.3.

Tablet of Example 2,

Time (hr)	0	1	2	3	4	5	6,
Elution rate (%)	0	11.7	31.6	50.5	65.8	77.1	86.1.

Tablet of Example 3,

Time (hr)	0	1	2	3	4	6	8,
Elution rate (%)	0	19.8	42.7	65.3	79.3	93.8	95.2.

Tablet of Example 4,

Time (hr)	0	1	2	3	4	6	8,
Elution rate (%)	0	9.0	21.2	40.8	55	77.9	90.7.

Tablet of Example 5,

Time (hr)	0	1	2	3	4	6	8
Elution rate (%)	0	7.4	19.6	36.3	50.2	75.4	92.6,

[Table 2].

Tablet of Example 6,

Time (hr)	0	1	2	3	4	6	8,
Elution rate (%)	0	4.6	11	20.1	30.3	49.5	67.7.

Tablet of Example 7,

Time (hr)	0	1	2	3	4	5	6,
Elution rate (%)	0	35.8	72.7	86.1	112	104	106.

Tablet of Example 8,

Time (hr)	0	1	2	3	4	5	6,
Elution rate (%)	0	13.7	37.4	54.8	77	88.3	88.9.

Tablet of Example 9,

Time (hr)	0	1	2	3	4	5	6,
Elution rate (%)	0	16.8	38.9	57.7	84.6	86.8	92.6.

Tablet of Example 10,

Time (hr)	0	1	2	3	4	5	6,
Elution rate (%)	0	19.1	35.6	45.9	59.2	60.9	65.2.

Tablet of Example 11,

Time (hr)	0	1	2	3	4	5,
Elution rate (%)	0	20.1	50.0	79.6	91.4	95.9.

Tablet of Example 12,

Time (hr)	0	1	2	3	4	5,
Elution rate (%)	0	28.7	63.3	92.5	98.1	99.9.

Is clear from the aforesaid [table 1] and [table 2] that the tablet of Reference Example 1 eluted by 100 % in 0.75 hours, whereas the tablets of Examples 1-12 had sustained-release property.

Compound B used in the following Examples 17-19 and Reference Example 2 was 3-chloro-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine, and the compound produced by the same process as in process in accordance with the following Synthesis Examples 1-5 was used.

Production of 3-chloro-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-2-(succinimidomethyl) thieno [2,3-b:5,4-c'] dipyridine.

Synthesis Example 1

Acetonitrile (48 g) was added dropwise at 70° C to a mixture of hexane solution of 1.6 M n-butyllithium (728 ml) and tetrahydrofuran (900 ml). It was stirred at -70° C for 20 minutes, and thereafter, 4-methoxybenzoyl chloride (100g) dissolved in tetrahydrofuran (200 ml) was added dropwise at the same temperature. The reaction mixture was stirred at the same temperature

furthermore for 30 minutes, thereafter, it was acidified with 4 N hydrochloric acid. It was stirred at room temperature for 30 minutes, and precipitated crystals were recovered by filtration, and ω-cyano-4-methoxy acetophenone (69 .5 g, 68 %) was obtained. It was recrystallised from ethanol. Colourless prism crystals. mp. 127-128° C.

Synthesis Example 2

The compound obtained in Synthesis Example 1 (40 g), sulfur (8 g), 1-benzyl-4-piperidone (43.2 g), morpholine (19.9 g) and mixture of 2-propanol (1000 ml) were stirred at 70° C for five hours. The reaction mixture was left to stand at room temperature overnight. The precipitated crystals were recovered by filtration and were washed with 2-propanol, and 2-amino-6-benzyl-3-(4-methoxybenzoyl)-4,5,6,7-tetrahydrothieno [2,3-c] pyridine (52.4 g, 61 %) was obtained. It was recrystallised from ethyl acetate-hexane. Yellow prism crystals. mp. 164-165° C.

Synthesis Example 3

To the mixture of compound obtained in Synthesis Example 2 (8 g), 1,3-dichloroacetone (5.4 g) and tetrahydrofuran (140 ml), was added aluminum chloride (6.5 g) under ice cooling, and thereafter, it was refluxed for two hours 30 minutes. It was discharged while stirring the reaction mixture in toluene (100 ml) - water (100 ml). Toluene layer was washed with water, and the solvent was eliminated by distillation under reduced pressure after dried (MgSO4). 7-benzyl-3-chloro-2-chloromethyl-5,6,7,8-tetrahydro-4-(4-methoxyphenyl) thieno [2,3-b:5,4-c'] dipyridine (8.2 g, 83 %) was obtained. It was recrystallised from ethanol.

mp. 194-195° C.

Synthesis Example 4

The mixture of compound obtained in Synthesis Example 3 (13.9 g), succinic acid imide (4.4 g), potassium carbonate (6.2 g) and N,N-dimethylformamide (140 ml) were stirred at 70° C for two hours, and thereafter, it was discharged to water, and extraction was carried out with ethyl acetate. The ethyl acetate layer was washed with water, and concentration was carried out under reduced pressure.after having done dried (MgSO4). The residue was subjected to silica gel column chromatography, and from the fraction eluted with ethyl acetate-hexane (1:1, v/v) 7-benzyl-3-chloro-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-2-(succinimide methyl) thieno [2,3-b:5,4-c'] dipyridine (21 g, 58 %) was obtained. It was recrystallised from tetrahydrofuran - isopropyl ether. Colourless prism crystals. mp. 241-243° C.

Synthesis Example 5

The mixture of compound obtained in Synthesis Example 4 (14.5 g), formic acid (29.1 ml), 10 % palladium carbon (50 % hydrated compound, 14.5 g) and methanol (500 ml) was stirred at room temperature for 21 hours. The catalyst was separated by filtration, and thereafter the filtrate was concentrated under reduced pressure. The residue was neutralized with saturated aqueous sodium bicarbonate and extraction was carried out with ethyl acetate. The ethyl acetate layer eliminated by distillation solvent after washing with water, dried (MgSO4), and the residual material was subjected to silica gel column chromatography. From the fraction eluted with ethyl acetate-methanol (10:1, v/v), ccompound B (5.0 g, 42 %) was obtained. It was recrystallised from ethyl acetate-methanol. Colourless prism crystals. mp. 225-226° C.

Example 17

Compound B 160mg, hydroxypropyl methyl cellulose (grade TC-5MW, made by Shin-Etsu Chemicals Co. Ltd.) 689.6 mg, crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 96 mg, light anhydrous silicic acid 4.8 mg and magnesium stearate 9.6 mg were weighed, and it was mixed with mortar. This mixed powder 300 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2, and, with 9.5 mm phi punch, and tablet was produced.

Examples 18-19

Compound B 160mg, hydroxypropyl methyl cellulose (grade TC-5EW, made by Shin-Etsu Chemicals Co. Ltd.) 497.6 mg, crystalline cellulose (grade Avicel PH101 made by Asahi Chemical Industry Co. Ltd.) 96 mg, light anhydrous silicic acid 4.8 mg, magnesium stearate 9.6 mg and lactose (Example 18) or sorbitol (Example 19) 192 mg was weighed, and it was mixed with mortar. This mixed powder 300 mg was weighed, and universal testing machine (Shimazu Corporation) was used, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2, and, with 9.5 mm phi punch, and tablet was produced.

Reference Example 2

Compound B 0.5g, lactose 2.21 g, corn starch 0.4 g were mixed with mortar, and thereafter, aqueous solution 0.7 g including hydroxypropylcellulose 0.1 g were added, and kneading was carried out. Kneaded material was dried under vacuum at 40° C for 16 hours, it was pulverised with mortar, and graded powder was made. Crosscarmellose sodium 0.16 g and magnesium stearate 0.016 g were mixed to the graded powder 2.96 g. This mixed powder 170 mg was weighed, and using universal testing machine (Shimazu Corporation), and it was tabletted with compression pressure 1.0 ton/cm2, and, with 9.5 mm phi punch, and tablet was produced.

Experimental Example 3.

One tablet each obtained in Example 17-19 and Reference Example 2 was accurately weighed, and using 0.3 % sodium lauryl sulfate aqueous solution 900 ml, the test was carried out at 50 rpm by paddle method. 1 ml was sampled with time and was filtered with membrane filter of 0.45 μm, and 0.2 ml were diluted with mobile phase 0.8 ml, and, sample solution was made. Separately, compound B was weighed precisely, and solution of 0.62 mg/mL was prepared, and it was diluted in the same way as in the sample solution, and standard solution was produced. Standard solution and sample solution 20 μl were measured by liquid chromatography. From the standard solution, concentration of sample solution was determined, and the elution rate was calculated. The results are shown in [table 3].

[Table 3],

Tablet of Reference Example 2,

Time (hr)	0	0.25	0.5	0.75	1,
Elution rate (%)	0	55.5	88.6	97.9	100.6.

Tablet of Example 17,

Time (hr)	0	0.5	1	2	3	4	5
Elution rate (%)	0	4.6	11.4	25.2	34.4	51.7	61.0.

Tablet of Example 18,

Time (hr)	0	0.5	1	2	3	4	5,
Elution rate (%)	0	8.8	20.5	41.4	56.0	75.8	82.8.

Tablet of Example 19,

Time (hr)	0	0.5	1	2	3	4	5,
Elution rate (%)	0	18.6	44.8	77.0	85.6	90.3	91.5.

Possible Applications in Industry

Because oral preparation of this invention has excellent sustained-release, blood concentration is smoothened, and it can be used advantageously as sustained-release oral preparation with persistence of effect, and prevention of side effect.

Moreover as for the oral preparation of this invention, the fluidity of granulated substance is good in production thereof, therefore, tabletting properties are increased.

Moreover, because gel-forming substance, also in accordance with requirements disintegration aid are contained in the preparation, the release of drug is controlled and more particularly it cacn be made for gradual release.

Patent Claims

1. A sustained release oral preparation containing (1) quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives and (2) a gel forming substance.

2. A preparation in accordance with Claim 1, wherein the quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives have antiinflammatory action or antirheumatic action.

3. A preparation in accordance with Claim 1, wherein a disintegration aid is further contained.

4. A preparation in accordance with Claim 1, wherein the gel forming substance is a water-soluble polymer compound.

5. A preparation in accordance with Claim 4, wherein the water-soluble polymer compound is a cellulose derivative, polyvinyl-series polymer compound or polyalcohol.

6. A preparation in accordance with Claim 4, wherein the water-soluble polymer compound is hydroxypropylmethylcellulose.

7. A preparation in accordance with Claim 3, wherein the disintegration aid is a saccharide.

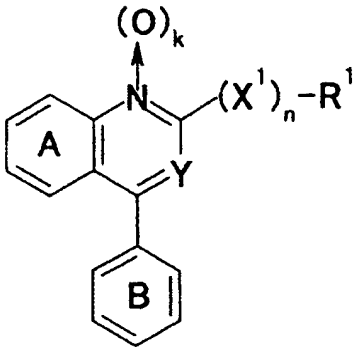
8. A preparation in accordance with Claim 7, wherein the saccharide is a sugar alcohol.

9. A preparation in accordance with Claim 1, wherein (1) quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives : (2) gel forming substance is about 1 : about 0.1-100 by weight ratio.

10. A preparation in accordance with Claim 3, wherein (1) quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives : (2) gel forming substance : (3) disintegration aid is about 1 : about 0.1-50 : about 0.01-50 by weight ratio.

11. A preparation in accordance with Claim 1, wherein the gel forming substance is formulated by about 10 wt.% or more with respect the whole preparation.

12. A preparation in accordance with Claim 1, wherein the quinoline or quinazoline derivative is a compound represented by formula



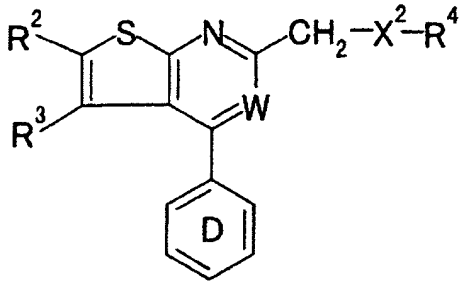
[I]

[in the formula, Y denotes a nitrogen atom or C-G (G denotes a carboxyl group which may be esterified or amidated, optionally substituted acyl group, optionally protected hydroxyalkyl group or halogen atom), R1 denotes an optionally substituted hydrocarbon group or optionally substituted heterocyclic group, X1 denotes an oxygen atom or optionally oxidised sulphur atom, n denotes 0 or 1, k denotes 0 or 1. G and R1 may be linked to each other to form a ring. Ring A and Ring B may each have substitute group] or a salt thereof.

13. A preparation in accordance with Claim 12, wherein the Y is C-G'' (G'' denotes a carboxyl group which may be esterified), R1 denotes a C1-4 alkyl group substituted with an optionally substituted nitrogen-containing unsaturated heterocyclic group (wherein, it is bonded to said C1-4 alkyl group at the nitrogen atom constituting nitrogen-containing unsaturated heterocyclic group), n is 0.

14. A preparation in accordance with Claim 13, wherein the quinoline or quinazoline derivative is ethyl 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(1,2,4-triazol-1-ylmethyl) quinoline-3-carboxylate.

15. A preparation in accordance with Claim 1, wherein the thienopyridine or thienopyrimidine derivative is a compound represented by formula



[II]

[in the formula, R2 and R3 may be the same or different and denote a hydrogen atom, halogen atom or optionally substituted alkyl group, R2 and R3 may be linked to form an optionally substituted 5-7-membered ring. W denotes a nitrogen atom or a group represented by C-G' (wherein, G' denotes a

carboxyl group which may be esterified or halogen atom), X2 denotes an oxygen atom, optionally oxidised sulphur atom or a group represented by formula -(CH2)q- (wherein, q is an integer of 0-5), R4 denotes an optionally substituted heterocyclic group or optionally substituted amino group. The D ring may be substituted], or a salt thereof.

16. A preparation in accordance with Claim 15, wherein in the thienopyridine or thienopyrimidine derivative, R2 and R3 is linked to form an optionally substituted 5-7-membered ring, W is a group represented by C-G' (wherein, G' denotes a carboxyl group which may be esterified or halogen atom), R4 is an optionally substituted heterocyclic ring.

17. A method of release control of quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives by formulation of a gel forming substance in an oral preparation containing quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives.

18. The use of a gel forming substance for the production of a sustained release preparation containing quinoline or quinazoline derivatives, or thienopyridine or thienopyrimidine derivatives.

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